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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	David A. Cheresh et al.	)	
Application No.	09/538,248	)	
Filed:	March 29, 2000	)	Group Art Unit: 1652
For:	METHODS USEFUL FOR TREATING VASCULAR LEAKAGE AND EDEMA USING SRC OR YES TYROSINE KINASE INHIBITORS	)	
Examiner:	Rebecca E. Prouty	)	Attorney Docket No. TSRI 651.3

RESPONSE UNDER RULE 116

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Commissioner for Patents
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Sir:

This communication is submitted in response to the Office Action dated August 13, 2004 on the above-identified application.

Claims 1-4, 17-20, 32 and 33 are currently under consideration.

Claims 1-3 and 17-20 specify that the pharmaceutical composition comprises an inhibitor of human c-Src tyrosine kinase. Claim 4 is dependent on claim 3 and specifies that the inhibitor is PP1.

Claim 32 is dependent on claim 18 and specifies that the inhibitor is PP2.

Claim 33 is dependent on claim 3 and specifies that the inhibitor is PP2.

The rejection of claims 1, 2, 17 and 18 under 35 U.S.C. 102(e) as allegedly being anticipated by US 6,001,839 ("Calderwood Patent") is not warranted. As pointed out in prior Response, the Calderwood Patent teaches that certain pyrrolopyrimidine compounds, not pyrazolopyrimidine compounds, are useful for treating VEGF mediated edema. This patent only generally mentions the Src family of tyrosine kinases along with other classes of kinases (i.e., the Syk and Janus families, at col. 12, line 53, through col. 13, line 9). The present claims are limited to methods and articles of manufacture including inhibitors of

human c-Src, a specific member of the Src family of tyrosine kinases. In the portion of the patent that discusses determination of the *in vitro* potency of the pyrrolopyrimidine inhibitors (col. 18, line 28, through col. 19, line 18), the Calderwood Patent teaches an assay for Lck (a Src family inhibitor) and Zap (a Syk family inhibitor), but does not mention human c-Src. The Calderwood Patent does not teach or suggest that the pyrrolopyrimidine compounds are inhibitors of human c-Src. The selectivity of tyrosine kinase inhibitors is highly unpredictable with large variability in selectivities and activities depending on the spacial arrangement of substituents (see, for example, McMahon et al., Current Opin. in Drug Discov & Devel. 1(2):131-146 (1998), particularly at page 142 under heading "Summary and outlook;" copy previously submitted).

Furthermore, the Calderwood Patent is not enabling for a method of ameliorating tissue damage related to vascular leakage or edema comprising contacting said tissue with a vascular permeability modulating amount of a pharmaceutical composition comprising a human c-Src tyrosine kinase inhibitor, as claimed in the present application. The Calderwood Patent merely contains a *general* teaching that the compounds are tyrosine kinase inhibitors, and specifically teaches that certain of the compounds are Lck inhibitors (col. 19, lines 12-14). The patent states that the pyrrolopyrimidines may be useful in treatment of "VEGF mediated edema," but provides no teaching whatsoever that an inhibitor of human c-Src would have such utility. No activity data are presented in this patent for any of the inhibitors disclosed, against any tyrosine kinase. There is nothing in the patent that would enable one of ordinary skill to practice the methods and articles of manufacture claimed in the present application. Accordingly, the Calderwood Patent is not enabling for the methods and articles of manufacture of claims 1, 2, 17 and 18.

Burchat et al. (2000) has a date subsequent to the filing date of the present application, has not been applied against claims 1, 2, 17 and 18 and thus does not support the present rejection. Moreover, Burchat et al. does not show inhibition of human c-Src in any event. The last line of the Burchat et al. (2000) Abstract merely states that "Compound 1 is orally active in animal models" (emphasis added). Burchat et al. (2000) also does not cure all of the noted deficiencies of the Calderwood Patent as a reference against the present claims.

For the reasons stated above, the Calderwood Patent does not anticipate claims 1, 2, 17 or 18. This ground for rejection should be withdrawn.

The rejection of claims 1, 2, 17 and 18 under 35 U.S.C. 102(e) as allegedly being anticipated by US Patent Application No. 2003/0187001 ("Calderwood Application") is likewise not warranted. The Calderwood Application teaches that certain pyrrolopyrimidine compounds are useful for treating VEGF mediated edema at paragraph 101; however, it does not teach that inhibitors of human c-Src have such activity. Rather, paragraph 101 states that *KDR* tyrosine kinase is useful for inhibiting vascular permeability and edema.

In paragraph 53, this application only generally mentions the Src family of tyrosine kinases along with other classes of kinases (i.e., the Syk, Tec, Csk, Jak, Map, and Nik families). In paragraph 53, the examples of Src kinases listed in the parenthesis are Ick [sic], blk and lyn, but not human c-Src. Similarly the laundry list of kinases in paragraph 111 lumps Src together with at least six other families of inhibitors.

The present claims are limited to methods and articles of manufacture including inhibitors of human c-Src, which is not mentioned in the Calderwood Application. In the portion of the patent that discusses determination of the *in vitro* potency of the pyrrolopyrimidine inhibitors (col. 18, line 28, through col. 19, line 18), the Calderwood Application teaches an assay for Lck (a Src family inhibitor) and Zap (a Syk family inhibitor), but does not mention human c-Src. The Calderwood Application does not teach or suggest that the pyrrolopyrimidine compounds are inhibitors of human c-Src as required by all of the present claims. The selectivity of tyrosine kinase inhibitors is highly unpredictable with large variability in selectivities and activities depending on the spacial arrangement of substituents (see, for example, McMahon et al., discussed above).

Additionally, the Calderwood Application is not enabling for a method of ameliorating tissue damage related to vascular leakage or edema comprising contacting said tissue with a vascular permeability modulating amount of a pharmaceutical composition comprising a human c-Src tyrosine kinase inhibitor, as claimed in the present application. The Calderwood Application merely contains a *general* teaching that the compounds are tyrosine kinase inhibitors, and specifically teaches that certain of the compounds are *KDR* inhibitors that can be used to treat edema (paragraph 101), not inhibitors of human c-Src, as required by

all of the present claims. No activity data are presented in this application for any of the inhibitors disclosed in the application, against any tyrosine kinase. There is nothing in the application that would enable one of ordinary skill to practice the methods and articles of manufacture claimed in the present application.

Burchat et al. (2000) has a date subsequent to the filing date of the present application, has not been applied against claims 1, 2, 17 and 18 and thus does not support the present rejection. Moreover, Burchat et al. does not show inhibition of human c-Src in any event. The last line of the Burchat et al. (2000) Abstract merely states that "Compound 1 is orally active in animal models" (emphasis added). Burchat et al. (2000) also does not cure all of the noted deficiencies of the Calderwood Application as a reference against the present claims.

Accordingly, the Calderwood Application does not anticipate method claims 1 and 2 and article of manufacture claims 17 and 18, and this ground for rejection also should be withdrawn.

The rejection of claims 1, 2, 17 and 18 under 35 U.S.C. 102(e) as allegedly being anticipated by US Patent Application No. 2002/0156081 ("Hirst et al.") is likewise traversed. Hirst et al. do not provide an enabling disclosure of the presently claimed invention nor do the Calderwood Patent and the Calderwood Application as explained hereinabove. Treatment of edema is discussed by Hirst et al. only generally, in a laundry list shown in paragraph 315 of Hirst et al. In paragraph 350, Hirst et al. state that some of the compounds can be used to treat edema. Of the over 950 examples of compounds presented in Hirst et al. there is not a single data point of inhibition data. Only general allusions to unspecific activity against various diverse classes of tyrosine kinases are provided, as in paragraph 311. There is no specific teaching in Hirst et al. that an inhibitor of human c-Src can be used to treat vascular leakage and edema, as required by all of the present claims.

Burchat et al. (2002) has a date after the filing date of the present application, has not been applied against claims 1, 2, 17 and 18, and thus does not support the present rejection.

Accordingly, Hirst et al. cannot anticipate method claims 1 and 2 and article of manufacture claims 17 and 18.

Claims 3, 4, 19 and 20 stand rejected as being obvious over the Calderwood Patent, the Calderwood Application and Hirst et al. in view of Hanke et al. The present rejection of these claims is but a restatement of the prior rejection. Claims 3 and 4 are directly or indirectly dependent on claims 1 and 2, as is claim 32. Claims 19 and 20 are either directly or indirectly dependent on claims 17 and 18, as is claim 33. Neither the Calderwood Patent, the Calderwood Application, nor Hirst et al. discloses the invention defined by claims 1, 2, 17 and 18, as noted above. Moreover, none of these references disclose the pyrazolopyrimidine inhibitors PP1 and PP2, which are called for by claims 3, 4, 19, 20, 32 and 33. Hanke et al., while disclosing PP1 and PP2, does not disclose or suggest treatment of vascular leakage and edema utilizing an inhibitor of human c-Src as required by the present claims. Hanke et al. does demonstrate, however, that one inhibitor can have a wide variance in activity against different tyrosine kinases (see Table I on page 698). Hanke et al. would not have provided any motivation whatsoever to one of ordinary skill to use PP1 or PP2 to ameliorate tissue damage due to edema or vascular permeability. At most, the teachings of Hanke et al. are but an invitation to experiment that does not vitiate patentability.

The contentions that there is a structural similarity between the compounds disclosed in the Calderwood Patent and Calderwood Application to PP1 and PP2, and that this structural similarity would have motivated one of skill in the art to use PP1 and PP2 to treat edema as described in the Calderwood references and Hirst et al., is without merit. The alleged structural similarity between the Calderwood compounds and PP1/PP2 is superficial at best. These are clearly different chemical compounds. Pyrazolopyrimidines are not pyrrolopyrimidines and vice versa. As is evident from Hanke et al. and McMahon et al. discussed above, inhibition of tyrosine kinases is highly unpredictable. Small changes in structure can lead to large changes in activity and selectivity. The compounds of the Calderwood references are pyrrolopyrimidines, whereas PP1 and PP2 are pyrazolopyrimidines. The additional nitrogen in PP1 and PP2 relative to the Calderwood compounds could have a significant effect on activity and selectivity. In addition, the Calderwood compounds have a bulky phenoxy substituent on the phenyl ring, whereas PP1 and PP2 have relatively small methyl and chloro substituents on the phenyl ring. These differences could have significant effects on the binding affinity and selectivity of the

inhibitors, particularly since the compounds bind to specific binding pockets in the enzymes (see McMahon et al., page 135, paragraph bridging column 1 and column 2). Accordingly, one of ordinary skill in the art in March 2000 would not have had a reasonable expectation of success in using PP1 and PP2 of Hanke et al. to treat edema. Moreover, there is no suggestion in Hanke et al. that PP1 and/or PP2 are human c-Src inhibitors.

Regarding claims 19, 20 and 32, In re Ngai, 70 U.S.P.Q. 1862, is readily distinguishable. The prior art in that case already taught a kit and the necessary 10X buffer therefor. That is not the situation here. The specific composition containing human c-Src tyrosine kinase inhibitor and capable of modulating vascular permeability increase as defined by these claims is not in the prior art, neither is a packaged version of that composition as claimed. The new printed matter unquestionably conveys new utility, a new feature, to the package, not previously known to one of ordinary skill in the art.

For the foregoing reasons, none of the presently pending claims are either anticipated or rendered obvious by the applied references. Reconsideration and early allowance of all claims is earnestly solicited.

Respectfully submitted,

November 17, 2004

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